Immune Globulin Intravenous (Human)

Clinical Trial Design

For Primary Immune Deficiency

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Plasma Fractionation: Conclusions from BPAC Mar. 99

- Multi-step process
- Variations can have far-reaching effects on safety and efficacy
- Each product should be regarded as unique and Immune Globulin should not be treated as a single generic biologic.

Previous FDA Proposal: IGIV Trials (BPAC, Mar. 99)

- A Prospective, Double-Blinded, Randomized, Phase III Study.
- Evaluation of efficacy and safety of new IGIV products in comparison to a licensed IGIV product.
- Sample size = 80 patients per arm

Problems with this Trial Design

- Limited numbers of patients with PID that can be recruited for trials
- Multiple new IGIV Products to be tested
- Potential shortage of IGIV.

New Proposal (BPAC Mar. 2000): Background

- Discussion of possible trials that would reduce the sample size (internal, IDF)
  - PK studies
  - surrogate endpoints e.g. fever
- Justification for using historical controls
  - IGIV products have been very successful in limiting infections in PID patients
  - acute bacterial infections per patient per year = $\geq$ 4 without treatment, and $\leq$ 0.5 on treatment

New Proposal: Study Design

- Single-arm, 12 month (seasonal), open study
- Compare to historical controls for safety, PK, and efficacy
  - 80% power
  - 99% confidence (alpha = 0.01)
  - one-sided testing

Clinical Trial Design: Safety

Safety targets are based on previous trials.

- Historical control = 20% AERs per infusion
- target for trial to exclude > 40% AERs (0.4 = 95% upper confidence limit, one sided)
- sample size ~ 50 patients receiving $\geq$ 12 infusions each

Clinical Trial Design: Efficacy

- Establish efficacy using an objective, clinically meaningful endpoint
  - primary endpoints: acute serious bacterial infections (pre-defined)
  - secondary endpoints: serum IgG levels, antibiotic treatment, hospitalizations, fever, etc.
- Sample size should be sufficient to determine whether the infection rate for the new IGIV is at or below the “beltline” (n ~ 50).

Clinical Trial Design: Efficacy (contd.)

- Primary endpoint: acute serious bacterial infections
  - infections per patient per year ≤ 0.5 on approved IGIV
  - data with new product must exclude infection rate ≥ 1 infection per patient per year

Types of Infection: positive bacterial cultures

- Bacteremia/sepsis
- Bacterial meningitis
- Osteomyelitis/septic arthritis
- Bacterial pneumonia
- Visceral abcess

Clinical Trial Design: PK Studies

- At least 20 patients
- Washout period (three x T1/2 on new product)
- C_{max}, T_{max}, AUC, Cl, and T1/2
- Trough levels for at least 5 T1/2s.
- Observed values should not be inferior to those concurrently or previously determined for approved products

Clinical Trial: FDA Review

- The trial would be considered a Phase III pivotal trial sufficient for licensure.
- FDA may consider Fast Track depending on the status of IGIV supply
- At this time there is no apparent shortage

Conclusions

- Number of patients per trial will be about 50, permitting concurrent trials of new products.
- For approval, the new product will need to have acceptable safety, PK and efficacy profiles when compared to historical standards.
- We encourage sponsors to collect data during the trials to validate surrogate markers (e.g. antibodies against specific pathogens relevant to PID).

Rate of IGIV Licensure

- 1996 - 2002 - No new IGIV's licensed
- 2003 - 2 (Gamunex, Flebogamma)
- 2004 - 1 (Octagam)